Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 35-52 are pending in the application, with claims 35, 43, 46 and 49 being the independent claims. Claim 33 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 35-52 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Support for New Claims

Support for new claims 35-52 can be found throughout the specification, for example, at page 7, lines 11-13, at page 25, line 8, through page 33, line 3, and in original claim 33.

II. Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 33 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *See* Paper No. 9, page 2. The basis for this rejection is the phrase "with the a region" found in claim 33. Claim 33 has been canceled. None of the

newly added claims include the phrase at issue. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph, is moot and should be withdrawn.

III. Claim Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 33 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. *See* Paper No. 9, page 2. According to the Examiner, the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *See* Paper No. 9, page 2. Applicants respectfully traverse this rejection.

Claim 33 has been cancelled. New claims 35-52 encompass subject matter which was encompassed by claim 33. Applicants submit that the subject matter of new claims 35-52 is fully enabled and that the rejection under 35 U.S.C. § 112, first paragraph, cannot properly be applied to the new claims.

The present invention is directed, in general, to the treatment or prevention of dementias of the Alzheimer's type of neuronal degeneration by interfering with AD7c-NTP expression at the level of transcription and/or translation. More specifically, the methods of the invention comprise administering to an animal in need thereof:

- an antisense oligonucleotide (claims 35-42);
- a ribozyme (claims 43-45);
- an oligonucleotide that forms one or more triple-stranded regions with the coding region of AD7c-NTP DNA (claims 46-48); and
- a ribonucleotide external guide nucleic acid molecule (claims 49-52).

The molecules used in the methods of the invention include nucleotide sequences that are complementary to or that correspond to nucleotides 150-1139 of SEQ ID NO:1.

The specification, along with the information available in the art, would have provided ample guidance for a skilled artisan to practice the presently claimed methods without undue experimentation. General information regarding the use of antisense oligonucleotides, ribozymes, triple helix-forming oligonucleotides, and ribonucleotide external guide nucleic acid molecules, for therapeutic purposes, is provided in the specification at page 28, line 20, through page 33, line 3. Additional information on the therapeutic use of these molecules would have been available to persons of ordinary skill in the art. Details regarding the appropriate route(s) of administration, methods for enhancing the cellular uptake of the molecules used in the methods of the invention, and the preparation of pharmaceutical formulations for use with the methods of the invention, would have been known by persons of ordinary skill in the art at the time of the effective filing date of the application. *See* Specification at page 30, line 14 through page 33, line 3. Thus, the practice of the claimed methods would not have required undue experimentation.

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). Applicants respectfully submit that the reasons set forth in

support of the rejection under § 112, first paragraph, are legally insufficient to establish a *prima facie* case of non-enablement.

According to the Examiner, "[t]he instant specification does not provide any specific guidance such as what particular antisense, ribozyme, external guide sequence, or tiplex forming oligonucleotide sequences could be used effectively in the claimed method." Paper No. 9, page 3. Applicants respectfully disagree. The specification sets forth the nucleic acid sequence of AD7c-NTP (SEQ ID NO:1). The claims specify that the molecules used in the practice of the methods are complementary to or correspond to nucleotides 150-1139 of SEQ ID NO:1. A skilled artisan would appreciate that antisense oligonucleotides, ribozymes, triple helix-forming oligonucleotides and ribonucleotide external guide nucleic acid molecules interfere with gene expression by recognizing complementary or corresponding nucleotide sequences and thereby inhibit transcription and/or translation. Based on the sequence information in the specification, and an understanding of the mechanisms by which antisense oligonucleotides, ribozymes, triple helix-forming oligonucleotides and ribonucleotide external guide nucleic acid molecules inhibit gene expression, a person of ordinary skill in the art would have been able to select the appropriate nucleotide sequences to effectively interfere with the expression of AD7c-NTP in an animal using the claimed methods.

The Examiner stated that "[t]he instant specification does not provide guidance or examples that would show by correlation what modes of delivery would predictable [sic] provide for a treatment of disease in general and for the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration in particular." Paper No. 9, page 3. Applicants respectfully disagree. The specification makes it clear that AD7c-NTP overexpression *in*

the brain is associated with Alzheimer's disease and neuronal degeneration. *See, e.g.*, Specification at page 41, lines 18-28 (showing significantly higher levels of AD7c-NTP mRNA in AD brains versus aged control brains). In addition, the specification indicates that:

> The NTP antisense oligonucleotide, NTP triple helix-forming oligonucleotide, NTP ribozyme or NTP EGS [external guide sequence], and the pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intra-peritoneal, transdermal, intrathecal or intracranial routes.

Specification at page 30, line 28, through page 31, line 3. Thus, a person of ordinary skill in the art would recognize that any mode of delivery that brings the compounds into contact with neuronal cells in an animal would be effective in the context of the present invention.

The Examiner also stated that: "[t]he instant specification does not provide any examples of inhibiting AD7c-NTP in cells in culture or in an animal or provide guidance that would show by correlation the treatment or prevention of Alzheimer's type of neuronal degeneration via the administration of antisense based nucleic acid compounds." Paper No. 9, pages 3-4. Applicants submit that the technological field of inhibiting gene expression by use of antisense oligonucleotides, ribozymes, triple helix-forming oligonucleotides and ribonucleotide external guide nucleic acid molecules, was sufficiently advanced at the time of the effective filing date of the application, and the mechanisms by which such molecules functioned was well established. Therefore, a person of ordinary skill in the art would have been able to practice the methods of the invention without undue experimentation, even in the absence of a working example.

There are many examples from the scientific literature that demonstrate successful therapeutic applications of the kinds of molecules that are used in the practice of the claimed methods. For example, several instances of the successful application of antisense molecules *in vivo* are described in Galderisi *et al.*, *J. Cell. Physiol. 181*:251-257 (1999) (copy attached hereto as Exhibit A). Among the examples provided in Galderisi are the following:

- Antisense oligonucleotides against protein kinase C alpha (PCK-α) mRNA produced clinical responses when administered to ovarian cancer patients. *See* Galderisi at page 253, bottom right column;
- Antisense oligonucleotides against c-raf mRNA produced "promising clinical response[s]" in patients with breast, prostate, and colon cancer. *See* Galderisi at page 254, top left column;
- Antisense oligonucleotides against bcr/abl mRNA, when administered to a patient with chronic myelogenous leukemia (CML), resulted in "complete hematological remission." *See* Galderisi at page 254, middle left column;
- Antisense oligonucleotides targeted against c-myc mRNA, when delivered into balloon-denuded porcine coronary arteries, caused a reduction in neointimal thickness (which is usually increased following balloon angioplasty). *See* Galderisi at page 254, right column; and
- Antisense oligonucleotides directed against the 5'-region of the preS gene of duck hepatitis B virus (DHBV), injected intravenously into DHBV-infected ducks, inhibited DHBV replication and caused a decrease in serum DHBV DNA levels. *See* Galderisi at page 255, left column.

In addition, Agrawal, *Tibtech. 14*:376-387 (1996) (cited by the Examiner at page 4 of the Office Action) states that "many reports have appeared in the literature confirming the application of antisense technology in *in vivo* models." Agrawal at page 376, bottom left column. Agrawal goes on to describe eight specific examples where antisense technology has been successfully applied in animals. *See* Agrawal at page 376, paragraph bridging left and right columns.

The above-described examples support the enablement of the invention in two respects. First, the general techniques used in these examples were available as of the effective filing date of the application. In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, an Applicant need not supply information that is known in the art. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997). The examples set forth above, therefore, would have supplemented the teachings of the specification and would have provided additional guidance to those of ordinary skill in the art in practicing the currently claimed methods.

Second, the examples clearly demonstrate that antisense technologies, in general, can be used to successfully disrupt gene expression and can provide positive clinical outcomes. Since the antisense techniques used in the examples set forth above were effective, there is no reason to believe that such techniques would not be equally effective when used in the context of the present invention, *i.e.*, in targeting/disrupting AD7c-NTP expression.

The Examiner has cited three references that discuss various technical considerations related to the use of antisense molecules. Agrawal, *Tibtech. 14*:376-387 (1996) is cited for the proposition that "[o]ligonucleotide must be taken up by cells in order to be effective." Paper No. 9, page 4 (quoting Agrawal at page 378, bottom left column). The specific

portions of Agrawal cited in the Office Action relate to the cellular uptake of oligonucleotides *in culture*. *See* Agrawal at page 378, bottom left column, through page 379, middle left column (under the heading "Cell culture system and target gene"). Agrawal concludes, however, that "[i]t is clear from some of the studies mentioned in this review and many other published reports that PS-oligonucleotides show more sequence-specific antisense activity in animal models than in cell culture experiments." Agrawal at page 384, middle right column. The present invention relates to the administration of antisense oligonucleotides, ribozymes, triple helix-forming oligonucleotides and ribonucleotide external guide nucleic acid molecules *to animals*, not to cells in culture. Thus, the concerns with cellular uptake of oligonucleotides in cell culture, as discussed in Agrawal, are irrelevant with respect to the claimed methods. Importantly, Agrawal indicates that antisense technology *is* effective in animals, thereby supporting Applicants' position that the claimed methods are fully enabled.

The Examiner cited Branch, *TIBS 23*:45-50 (1998), for issues relating to "non-antisense effects" and accessibility of oligonucleotides to target RNA. With respect to "non-antisense effects" it is important to recognize that Branch's comments relate to the ability of an antisense molecule to precisely recognize one specific target and none others. It is noted by Branch, however, that "both ODNs [antisense oligonucleotides] and bioengineered ribozymes can undeniably hit their intended targets." Branch at page 45, bottom right column. Branch also notes that, in the pharmaceutical context, non-antisense effects may be advantageous. *See* Branch at page 46, middle left column ("Phase III clinical trials of ISIS 2922, a phosphorothioate oligonucleotide (S-ODN) that induces both antisense and non-antisense effects, are also under way in patients with cytomegalovirus-associated

retinitis. It is hoped that this compound's diverse mechanisms of action will yield a single drug that provides many of the benefits of combination therapy." (internal citations omitted)). Most of the concerns about "non-antisense effects" discussed in Branch relate to non-antisense effects in research settings, not in therapeutic settings. *See* Branch at page 46, middle left column. Thus, the potential for "non-antisense effects" does not support the conclusion that the present invention is not enabled.

With respect to oligonucleotide accessibility, Branch simply indicates that not all oligonucleotides are equal in their ability to bind to a particular RNA target, and that screening may be needed to identify optimal sequences. In the context of the enablement requirement, experimentation, even complex experimentation, is not undue if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *see also Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Screening for oligonucleotides with enhanced accessibility to a target would not be regarded as undue experimentation.

As noted by Branch, "[o]ne approach [to enhance specificity within cells] has been to deploy multiple antisense compounds, each directed against a different site in the same target RNA and thereby achieve annihilation by molecular triangulation." Branch at page 48, bottom right column. Branch also describes examples in which researchers identified effective antisense oligonucleotides by screening multiple candidate oligonucleotides. *See* Branch at page 49, left and center columns. In one example, 1938 oligonucleotides were screened to identify those that could bind to a 122 nucleotide RNA representing the 5' end

of β-globin mRNA. *See* Branch at page 49, left column. In another example, an antisense oligonucleotide that was able to reduce the level of *c-raf* kinase mRNA by more than five-fold was identified by screening 34 candidate oligonucleotides. *See* Branch at page 49, paragraph bridging left and center columns, and Fig. 3. It is therefore clear that persons of ordinary skill in the art typically engaged in screening to identify effective antisense oligonucleotides and that such screening would not have been regarded as undue experimentation.

The statement in Branch at page 49, right column, that "[i]t is not yet clear whether *in vitro* screening techniques . . . will identify ODNs that are effective *in vivo*," does not indicate that such screening techniques would necessarily be ineffective or that they would be regarded as undue experimentation. As noted by Branch, "[i]f tests of 50 molecules identify good candidates, tests of thousands of compounds should identify better ones." Branch at page 49, right column. There has been no evidence presented to suggest that screening thousands of antisense oligonucleotides would have been regarded as undue experimentation. Thus, Branch does not support the assertion that the present invention is not enabled.

Moreover, at the time of the effective filing date of the application, computerized modeling of mRNA structure would have been available to persons of ordinary skill in the art to assist in the identification of mRNA targets. *See, e.g.*, Jaroszewski *et al.*, *Antisense Res. Dev. 3*:339-348 (1993) (abstract submitted herewith as Exhibit B). The selection of target sequences for antisense molecules using computer-based methods is discussed in Galderisi:

> Modeling of the secondary structure of the target mRNA by computer software can be used for target selection of

> antisense molecules. Such a method carefully considers the potential folding pattern of a chosen mRNA as derived from its particular nucleotide sequence. After determining the free energy of a given secondary structure, the most probable folding structures are indicated, showing open loops and bulges that are accessible for oligonucleotides for efficient hybridization.

Galderisi at page 252, bottom left column. The use of such computerized methods would have enabled persons of ordinary skill in the art to identify accessible regions in AD7c-NTP mRNA and design corresponding oligonucleotides.

Finally, the Examiner cited Jen and Gewirtz, *Stem Cells 18*:307-319 (2000), as indicating that "progress needs to be made in the art," and outlining the "key challenges" to the field. *See* Paper No. 9, pages 6-7. The need for progress, and the existence of "challenges," however, does not indicate that antisense-based methods would have required undue experimentation. Jen and Gewirtz does not support a finding of non-enablement.

In summary, there are many examples in the scientific literature showing the successful clinical use of antisense-based technologies in the treatment of various diseases and conditions. The methods used in these examples would have been available to persons of ordinary skill in the art at the time of the effective filing date of the present application and therefore would have supplemented the teachings in the specification to enable the practice of the claimed methods. The references cited in the Office Action, at best, highlight certain technical considerations to be addressed in practicing antisense-based methods. The references, however, do not demonstrate that the practice of the claimed methods would have required undue experimentation. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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